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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,091	11/21/2001	Joseph M. Fernandez	INVIT1120-3	1288

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EXAMINER

WESSENDORF, TERESA D

ART UNIT

PAPER NUMBER

1639

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/990,091

Applicant(s)

FERNANDEZ ET AL.

Examiner

T. D. Wessendorf

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 December 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 47, 57, 59-63, 71-73 and 76 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 47, 57, 59-63, 71-73 and 76 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

Claims 39-46, 48-56, 58, 64-70, 74-75 and 77-80 have been cancelled in the Amendment of 4/3/03.

Claims 47, 57, 59-63, 71-73 and 76 are under examination.

Oath/Declaration

The new oath or declaration overcomes the objection to the oath or declaration.

Specification

The amendments to the specification with respect to the abstract, trademark and incorporation of essential materials have overcome the objection to the specification.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47, 57, 59-63, 71-73 and 76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons advanced in the last Office action.

Response to Arguments

As a preliminary matter, as indicated in the telephonic conferences, the indicated allowability of the instant claims is regretted. While the rejection under 112 was not discussed however, this does not mean that such rejection would not be made. Upon review of the disclosure, it was noted that the specification describes only a method of making and not a method of use for the library. Hence, a rejection to this effect has been made. [Note this same rejection was given in the prior application 09/054,936, albeit, the instant application does not make reference to said 09/054,936 application.]

Applicants urge as an initial matter, that the claims are directed to methods of producing a "library of expressible open reading frames (ORFs)", and are not directed to the proteins encoded by such ORFs or directed to expressing the expressible ORFs. As such, it is submitted that the issues raised with respect to the likelihood (or not) that an encoded protein may be toxic would not appear to be relevant. Nevertheless, as urged, even if, for argument sake, it is considered that a protein encoded by an expressible ORF is expressed in a cell,

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and if it is further assumed that the expressed protein is toxic when expressed in the cell, the skilled artisan, desiring the encoded protein, would have known that it could be expressed using an in vitro translation, or transcription/translation system, as such systems were well known and routinely used in the art at the time the subject application was filed.

In response, contrary to applicants' arguments, the claims do not recite only the making of the library of expressible ORFs. The final step(e) claims the "expression vectors comprising ORFs in an orientation for expression of a polypeptide encoded by the ORF". If the claims were to recite only **expressible** ORFs without actually expressing the proteins encoded by said ORFs, the method would indeed have no use.

Applicants appear not to appreciate the rejection with respect to the toxic effect of the expressed proteins. The context by which it is questioned is with respect to the use of the expressible ORF library. As argued above, the claims are drawn only to the method of making expressible ORF and not to the expression thereof. Even if the library of expressible genes encodes different proteins, it does not positively recite whether this is the specific use of the library. The library of ORF can encode millions of proteins.

With respect to a "marker protein", Applicants again point out, as discussed above, that the claims are not directed to expressed proteins. As such, any potential toxicity of a marker protein would not appear to be directly relevant to the claimed subject matter. Further in this respect, Applicants point out that the claims do not refer to any marker protein or sequence encoding a marker protein as such this is irrelevant. Nevertheless, applicants state that the Gillies et al reference cited in the Background of the invention, which issued well before the priority date of the subject application (and itself has a priority date of March 1986) is directed to vectors and methods for overcoming such potential problems (see, e.g., Abstract). As such, the cited reference appears to solve any potential toxicity problem that may be associated with expression of a marker protein.

In reply, since the claims do not recite a marker, as argued then the arguments are irrelevant, as stated above.

It is argued that Eckert and Kunkel, cited in support of the rejection, describe fidelity rates of polymerase used in PCR and describe base substitution error rates. Applicants submit, however, that Table 1 (pages 18-84) of the subject application, which provides a library of expressible human ORFs produced according to a method of the invention, demonstrates that PCR

can be useful in the claimed method, despite the well known error rates associated with PCR. It is further submitted that Table 1 of the subject application provide substantial evidence that the claimed methods are enabled.

In response, Table 1 in the specification, lists the human proteins successfully expressed using the methodology, not a library of expressible human ORFs as argued.

With respect to a "use" of a library produced according to a method of the invention, it is submitted that the skilled artisan would recognize that such a library is useful as a research tool, for example, to characterize RNA molecules expressed in a particular cell type. It is argued that Sambrook et al, for example, recognize that cloning into prokaryotic vectors "has become a fundamental tool" of eukaryotic molecular biology. See page 16.2, regarding cloning in mammalian cells.

In reply, the specification does not recite the library as a research tool. As of the time of filing, the application is incomplete, as further studies are required to determine any specific or substantial use of said library.

Sambrook, as relied upon states "...These methods have been used to overproduce proteins for structural and biochemical studies and to identify elements involved in the control of gene

expression...." A patent is not a hunting license, it is a successful reward for the accomplishment of a search.

Applicants point out that the use of the recited enzymes to link nucleic acid molecules was well known in the art prior to the time the subject application was filed (see, e.g., U.S. Pat. No. 4,959,317, describing the use of loxp-cre to link nucleic acid molecules; U.S. Pat. No. 5,888,732 (claiming priority to at least June 1996), describing the use of lambda integrase to link nucleic acid molecules; and Ringrose et al., which, as stated by the Examiner in support of the obviousness rejection, describes "that FLP and Cre have been used extensively in a variety of organisms to engineer specific DNA rearrangement at defined sites".

In reply, as stated by applicants the enzymes are used to link nucleic acid molecules, not use for inserting, as claimed, into the expression vectors using these enzymes as in step c).

The specification, accordingly, has not taught how to use the claimed library of expressible ORFs.

Claims 47, 57, 59-63, 71-73 and 76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to Arguments

Applicants submit that one skilled in the art would have known how to "use an enzyme" for a purpose as recited in the claims, particularly the recited enzymes (see, e.g., U.S. Pat. No. 4,959,317; U.S. Pat. No.5,888,732; and Ringrose et al., as discussed above with respect to the enablement rejection).

Further, Applicants point out that Paragraph 31 of the subject application describes the recited enzymes, and discloses references relevant to the enzymes (see, also, claim 11 as originally filed). As such, it is submitted that the specification clearly describes how to use an enzyme as recited in the claims.

In response, as pointed out by applicants paragraph 31(?) of the instant disclosure describes only the enzymes but not what appears to insert the purified amplified ORFs, as claimed. The original claim 11 uses enzymes to ligate and cleave the DNA.

This function is not positively recited in the instant claims. Original claim 1, from which claim 11 ultimately depends, recites coding regions, not ORF or all the method steps in the present claim, specifically step c).

Applicants' arguments with respect to the inconsistency in the claim with respect to the added Seq. ID. 7 is noted. As stated by applicants, referring to paragraph 50 of the instant specification, Seq. 7 does not stand alone. Rather, it forms a part of the **common sequence** of Seq. ID. 1. The word comprising is an open-ended language that includes other sequences, not necessarily Seq. ID. 1 to which Seq. 7 is attached.

Applicants point out that claim 5 of the application as originally filed recites "wherein...the 3' primer causes the amplification product to end at the third position of the codon immediately preceding the stop codon." Applicants submit that "the third position of the codon immediately preceding the stop codon" is "just prior to a stop codon" and, therefore, would submit that the language of claim 71 does not broaden the specification. Nevertheless, in order to advance prosecution of the subject application, claim 71 has been amended to recite the language of original claim 5.

In response, newly amended claim 71 does not contain said limitation at the third position of the codon. Furthermore,

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original claim 1 is not the same as the present claim 71. The specification recites for a specific stop codon.

It is argued Table 1 discloses many protein families comprising proteins encoded by the exemplified human ORFs, including, for example, families of kinases (e.g., MAP kinases, see C5 at page 20; 169-16 at page 24; and 215-38 at page 26; and c-Jun kinases, JNK, see 215-2, 169-37, 169-25, and 167-16 at pages 69-70), of phosphatases (e.g., type 2 protein phosphatases, including type 2A, see C3, M428 E1, and M478 A1 at page 31, and M316 B1 and C7 at page 35, and type 2C phosphatases, see M465 A.6 at page 65), and of oncogenes (e.g., Ras related proteins, see M512 115 at page 33, (25 at page 68, M302 83 at page 74, C1 at page 75, and M312 F3 at page 78). Numerous additional families of proteins are evident upon inspection of Table 1, including, for example, families of growth factors, of G protein coupled receptors (e.g., 172 at page 19, 215-25 at page 28, 166-64, 166-88 and 166-76 at page 69, and M423 E5 at page 70), of heat shock proteins (e.g., M365 E4 at page 44, and M37 1 174 at page 52) and of ribosomal proteins (e.g., M22 D4, M314 E2, M266 F5, etc., at page 67). Applicants point out that the proteins exemplified in the above list for the various families are not exhaustive for each of the families, and that the exemplified families are only a fraction

of the total families disclosed in Table 1, including families comprising more closely related members as well as families comprising more distantly related members.

In reply, these families of proteins however, are encoded by a common Seq. ID 1 to which Seq. ID 7 is linked. And, not any sequences that can be included to Seq. ID. 7.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47, 57, 59-63, 71-73 and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Response to Arguments

The rejections of the claims have been partly overcome with the amendments to the claims and applicants' arguments. The rejections that have not been overcome are addressed below.

A). It is submitted that the skilled artisan would know that such an orientation would be with respect to promoter elements present in an expression vector.

In reply, if the orientation is relative to the promoter element, then the claim is not commensurate in scope therewith. It is not clear where in the specification said orientation is relative to the presence of the promoter element.

Newly amended claim 71, step (e) appears to be an incomplete sentence in reciting, "thereby producing a library of selected expressible."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 47, 57, 59-63, 71-73 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harney (U.S. 6,277,632) in view of Shuman (U.S. 5,766,891) or Ringrose et al (Eur. J. Biochem.) and Dubensky et al (U.S. 6,342,372) for reasons set forth in the Supplemental action.

Response to Arguments

[As applicants noted the rejection under 35 U.S.C. 103(a) was made in the Office Action mailed May 1, 2003, and that a

second such rejection was made in the Supplemental Office Action mailed July 7, 2003. However, the Supplemental Office action was in response to applicants' telephone conference with Supervisor, Andrew Wang. Applicants state in the teleconference that references in the Office action of 5/1/03 do not teach the Kosak sequence, CACC. Hence, the Supplemental action was issued.] Applicants point out that the cited references, either alone or in combination, do not teach or suggest amplifying DNA using a primer pair including a 5' primer comprising a nucleotide sequence starting 5'-CACCATG and a 3' primer which causes the amplification product to end immediately preceding a stop codon, as required by the claims.

In response, Shuman and Ringrose disclose the use of stop codons, the determination of which is well known in the art. Schuman states "RNA polymerase II, a downstream polyadenylation signal, the start codon AUG, and a termination codon for detachment of the ribosome. Such vectors may be obtained commercially or assembled from the sequences described by methods well-known in the art..." Thus, it will be well within the ordinary skill in the art to determine in commercially packaged vectors where the stop codon is located. That is, if the package does not contain instructions for said determination. Without a stop codon, amplification will have no

end. There is no teaching in the prior art where an amplification step has not been done to completion nor has a product not been obtained. As stated in the previous Office action, Dubensky provides the motivation for attaching the known Kozak sequence, CACC, to an oligonucleotide primer sequence i.e., efficient translational initiation referencing Kozak (Cell 44:283-292, 1986).

No claim is allowed.

Conclusion

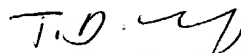
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-7924 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
March 20, 2004